CHAPTER 10

Amyloids identification based on fuzzy oil drop model

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Conceptual image showing the unrestricted capability for linear propagation of bands characterized by variable hydrophobicity (different degree of gray color). Dashed lines correspond to elongation beyond the boundaries of PDB structures.

The fuzzy oil drop model asserts the presence of a monocentric hydrophobic core described by a 3D Gaussian function. As previously shown, globular proteins tend to conform to this idealized distribution (with variable accuracy). In effect, the Gaussian describes an "ideal micelle", which, in accordance with information theory, contains very little information. This is due to its deterministic (symmetrical) structure, where the placement of all components can be predicted with high confidence (high probability means low information content).

Globular (or near-globular) proteins may be inscribed in 3D Gaussian capsules whose dimensions are adjusted to each case by manipulating their σ (sigma) coefficients. As previously discussed, such proteins may be treated as "intelligent micelles": in addition to adopting micelle-like conformations, they also encode specific information which is expressed as localized deviations from the theoretical distribution of hydrophobicity (note that such "improbable" structures may carry a substantial quantity of information).

From Globular Proteins to Amyloids
ISBN: 978-0-08-102981-7
https://doi.org/10.1016/B978-0-08-102981-7.00015-4

While there are many possible deviations from the monocentric model, one in particular is worth further analysis: we refer here to a strongly ordered system in which the hydrophobic core has been replaced by a linearly propagating sequence of "bands" (alternating between high and low hydrophobicity). This arrangement is observed in amyloids, and the present chapter provides arguments in support of defining an amyloid as a structure which exhibits this characteristic band-like pattern.

Another interesting property of amyloids is that rather than simply deviating from the Gaussian distribution, they may often be regarded as polar opposites thereof. This effect may be explained if we observe that in amyloid structures the actual distribution of hydrophobicity is determined by the intrinsic preferences of each participating residue, with no cooperative tendency to form a shared hydrophobic core (consistent with the Gaussian).

By assessing the specific discordance between theoretical (T) and observed (O) hydrophobicity distributions, we may formulate criteria for regarding a given structure as an amyloid.

Researchers often point to β-strands as being particularly prone to amyloid transformation. On the other hand, it can also be shown that amyloids may emerge from other types of structures − such as the tau protein [1]. Notably, the tau amyloid also satisfies the FOD-based amyloid identification criteria [2−4], which are presented below.

This chapter (10) is divided into three parts:

1. This part discusses the structure of amyloid forms of Aβ(1−42) chain fragments, based on PDB data.
2. In this part the Aβ(1−42) sequence is treated as a folding target (following the CASP procedure (http://predictioncenter.org)) in order to compare various alternative conformations for this polypeptide.
3. The specificity of sequence to generate characteristics secondary forms supporting globular of linear order is shown.

References

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